CHAPTER 29

Hodgkin's lymphoma

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In the year 2005, approximately 8,000 new cases of Hodgkin's lymphoma (HL) will be diagnosed in the United States. Over the past 4 decades, advances in radiation therapy and the advent of combination chemotherapy have tripled the cure rate of patients with HL. In 2005, more than 80% of all newly diagnosed patients can expect a normal, disease-free life span.

Epidemiology

Gender The male-to-female ratio of HL patients is 1.3:1.0.

Age The age-specific incidence of the disease is bimodal, with the greatest peak in the third decade of life and a second, smaller peak after the age of 50 years.

Race HL occurs less commonly in African-Americans (2.3 cases per 100,000 persons) than in Caucasians (3.0 per 100,000 persons).

Geography The age-specific incidence of HL differs markedly in different countries. In Japan, the overall incidence is low and the early peak is absent. In some developing countries, there is a downward shift of the first peak into childhood.

Etiology and risk factors

The cause of HL remains unknown, and there are no well-defined risk factors for its development. However, certain associations have been noted that provide clues to possible etiologic factors.

Familial factors For example, same-sex siblings of patients with HL have a 10 times higher risk for the disease. Patient-child combinations are more common than spouse pairings. Higher risk for HL is associated with few siblings, single-family houses, early birth order, and fewer playmates—all of which decrease exposure to infectious agents at an early age. The monozygotic twin sibling of a patient with Hodgkin's disease has a 99 times

It is known that identical twins of young patients with HL are much more likely to develop HL than fraternal twins and that interleukin-6 (IL-6) levels are increased in patients with HL and are correlated with a poor prognosis. This study found that unaffected identical twins of case subjects (surrogate case subjects) had an 88% higher IL-6 level than matched control subjects (P =.04). Some genetic polymorphisms of the IL-6 promoter were associated with low production of IL-6 and decreased risk of HL. Risk was decreased for both nodular sclerosis and other subtypes *(Cozen W, Gill PS, Ingles SA, et al: Blood 103:3216-3221, 2004)*.

A new study from Denmark pointed out a likely causal association between infectious mononucleosis-related EBV infection and the EBV-positive subgroup of young adults with HL. Only serologically confirmed infectious mononucleosis was associated with a persistently increased risk of HL. Of 29 tumors, 16 (55%) obtained from patients with infectious mononucleosis had evidence of EBV. There was no evidence of an increased risk of EBV-negative HL after infectious mononucleosis. In contrast, the risk of EBV-positive HL was significantly increased (relative risk: 4.0; 95% CI: 3.4 to 4.5). The estimated median incubation time from mononucleosis to EBV-positive HL was 4.1 years (95% CI: 1.8 to 8.3; *Hjalgrim H, Askling J, Rostgaard K, et al: N Engl J Med 349:1324-1332, 2004*).

higher risk of developing HL than a dizygotic twin sibling of a patient with HL. These associations suggest a genetic predisposition and/or a role for an infectious or environmental agent during childhood or early adolescence in the etiology of the disease.

Viruses Familial aggregation may imply genetic factors, but other epidemiologic findings mentioned previously suggest an abnormal response to an infective agent. Both factors may play a role in the pathogenesis of the disease. The Epstein-Barr virus (EBV) has been implicated in the etiology of HL by both epidemiologic and serologic studies, as well as by the detection of the EBV genome in 20%-80% of tumor specimens.

There have been no conclusive studies regarding the possible increased frequency of HL in patients with human immunodeficiency virus (HIV) infection. However, HL in HIV-positive patients is associated with an advanced stage and poor therapeutic outcome. (For further discussion of HL in patients with HIV infection, see chapter 27.)

Signs and symptoms

HL is a lymph node-based malignancy and commonly presents as an asymptomatic lymphadenopathy that may progress to predictable clinical sites.

Location of lymphadenopathy More than 80% of patients with HL present with lymphadenopathy above the diaphragm, often involving the anterior mediastinum; the spleen may be involved in about 30% of patients. Less than 10%-20% of patients present with lymphadenopathy limited to regions below the diaphragm. The commonly involved peripheral lymph nodes are located in the cervical, supraclavicular, and axillary areas; para-aortic pelvic and inguinal areas are involved less frequently. Disseminated lymphadenopathy is rare in patients with HL, as is involvement of Waldeyer's ring and occipital, epitrochlear, posterior mediastinal, and mesenteric sites.

Regular use of aspirin may be associated with a reduced risk of HL, according to a population-based, case-control study of 565 patients with HL and 679 control subjects. Regular analgesic use was defined as consumption of at least two tablets per week on average over the preceding 5 years. The risk of HL associated with regular aspirin use was significantly lower (OR = 0.60; 95% CI: 0.42 to 0.85) statistically than that associated with nonregular aspirin use. The investigators concluded that the inverse association between aspirin and HL suggests that NF-kappa-B signaling may play a key role in HL pathogenesis (*Chang ET, Zheng T, Weir EG, et al: J Natl Cancer Inst 96:305-315, 2004*).

Systemic symptoms About 30% of patients experience systemic symptoms. They include fever, night sweats, or weight loss (so-called B symptoms) and chronic pruritus. These symptoms occur more frequently in older patients and have a negative impact on prognosis (see section on "Staging and prognosis").

Extranodal involvement HL may affect extranodal tissues by direct invasion (contiguity; the so-called E lesion) or by hematogenous dissemination (stage IV disease). The most commonly involved extranodal site is the lungs. Liver, bone marrow, and bone may also be involved.

Diagnosis

The initial diagnosis of HL can only be made by biopsy. Because reactive hyperplastic nodes may be present, multiple biopsies of a suspicious site may be necessary. Needle aspiration is inadequate because the architecture of the lymph node is important for diagnosis and histologic subclassification.

The molecular signature of mediastinal large B-cell lymphoma (MLBCL) differs from that of other diffuse large B-cell lymphomas (DLBCLs) and shares features with classic HL. Investigators from Boston compared the gene expression profiles of newly diagnosed MLBCL and DLBCL and developed a classifier of these receptor signaling cascade, a profile resembling that of Reed-Sternberg cells of cHL. Like cHLs, MLBCLs also had high levels of expression of the interleukin-13 (IL-13) receptor and downstream effectors of IL-13 signaling, tumor necrosis factor (TNF) family members, and TNF receptor-associated factor-1 (TRAF1). These studies identified a molecular link between MLBCL and classic HL and a shared survival pathway (*Savage KJ, Monti S, Kutok JL ,et al: Blood 102:3871-3879, 2003).*

The prognostic significance of CD20-positive Reed-Sternberg cells in classic HL remains uncertain. Yet, a recent study from Memorial Sloan-Kettering Cancer Center (MSKCC) indicated that it is an indicator of poor response to standard chemotherapy. Of 248 patients with classic HL, 28 were CD20-positive. With a median follow-up of 30 months, significant prognostic factors in multivariate analysis were CD20 positivity, elevated WBC count, and low absolute lymphocyte count for time to treatment failure (TTF); and for overall survival (OS), CD20 positivity, elevated WBC count, bone marrow involvement, and age ≥ 45 years. Among 167 patients treated at MSKCC, both TTF ($P < .0001$) and OS ($P = .017$) were significantly decreased in CD20-positive patients. CD20-positive classic HL is a poor prognostic factor for TTF and OS. The authors recommended that all classic HL cases should be immuno-phenotyped for CD20 *(Portlock CS, Donnelly GB, Qin J, et al: Br J Haematol 125:701-708, 2004).*

Pathology

Reed-Sternberg cell

In a biopsied lymph node, the Reed-Sternberg (R-S) cell is the diagnostic tumor cell that must be identified within the appropriate cellular milieu of lymphocytes, eosinophils, and histiocytes. HL is a unique malignancy pathologically in that the tumor cells constitute a minority of the cell population, whereas normal inflammatory cells are the major cell component. As a result, it may be difficult to identify R-S cells in some specimens. Also, other lymphoproliferations may have cells resembling R-S cells.

The R-S cell is characterized by its large size and classic binucleated structure with large eosi-

nophilic nucleoli. Two antigenic markers are thought to provide diagnostic information: CD30 (Ber-H2) and CD15 (Leu-M1). These markers are present on R-S cells and their variants but not on background inflammatory cells.

Recent studies have confirmed the B-cell origin of the R-S cell. Single-cell polymerase chain reaction (PCR) analysis of classic R-S cells shows a follicular center B-cell origin for these cells with clonally rearranged but crippled V heavy-chain genes, presumably leading to inhibition of apoptosis. Also, high levels of the nuclear transcription factor-kappa-B (NF-κB) have been found in R-S cells; these high NF-κB levels may play a role in pathogenesis by interfering with apoptosis.

Histologic subtypes

According to the Rye classification (based on the number and appearance of R-S cells, as well as the background cellular milieu), there are four histologic subtypes of HL.

Nodular sclerosis, the most common subtype, is typically seen in young adults (more commonly in females) who have early-stage supradiaphragmatic presentations. Its distinct features are the presence of (1) broad birefringent bands of collagen that divide the lymphoid tissue into macroscopic nodules and (2) an R-S cell variant, the lacunar cell.

Mixed cellularity is the second most common histology. It is more often diagnosed in males, who usually present with generalized lymphadenopathy or extranodal disease and with associated systemic symptoms. R-S cells are frequently identified; bands of collagen are absent, although a fine reticular fibrosis may be present; and the cellular background includes lymphocytes, eosinophils, neutrophils, and histiocytes.

Lymphocyte-predominant HL is an infrequent form of HL in which few R-S cells or their variants may be identified. The cellular background consists primarily of lymphocytes in a nodular or sometimes diffuse pattern. The R-S variants express a B-cell phenotype (CD20-positive, CD15-negative). B-cell clonality has also been demonstrated by PCR of the immunoglobulin heavy-chain genes in single R-S variant cells in biopsy material from patients with lymphocyte-predominant HL.

This finding has led investigators to propose that lymphocyte-predominant HL is a B-cell malignancy with a mature B-cell phenotype, distinct from the other three histologic types of HL. Lymphocyte-predominant HL is often clinically localized, is usually treated effectively with irradiation alone, and may relapse late (a clinical feature reminiscent of low-grade lymphoma). The 15-year disease-specific survival is excellent (> 90%).

The World Health Organization (WHO) classification recognizes a new subtype of lymphocyte-rich classic HL that has morphologic similarity to nodular lymphocyte-predominant HL. However, the R-S cells have a classic morphology and phenotype (CD30-positive, CD15-positive, CD20-negative), and the surrounding lymphocytes are reactive T cells. This disease subtype does not show a tendency for late relapse and should be managed like other classic

Hodgkin's lymphoma histologies.

Lymphocyte depletion is a rare diagnosis, particularly since the advent of antigen marker studies, which led to the recognition that many such cases represented T-cell non-Hodgkin's lymphomas (NHLs). R-S cells are numerous, the cellular background is sparse, and there may be diffuse fibrosis and necrosis. Patients usually have advanced-stage disease, extranodal involvement, an aggressive clinical course, and a poor prognosis.

Staging and prognosis

Precise definition of the extent of nodal and extranodal involvement with HL according to a standard staging classification system is critical for selection of the proper treatment strategy.

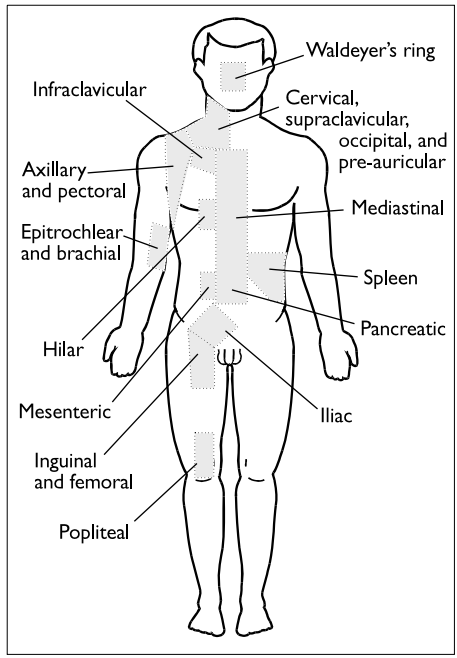

FIGURE 1: Anatomic regions for staging of Hodgkin's lymphoma

Staging system

The staging system is detailed in Table 1, and the anatomic regions that provide the basis for the staging classification are illustrated in Figure 1. The assignment of stage is based on:

- the number of involved sites
- whether lymph nodes are involved on both sides of the diaphragm and whether this involvement is bulky (particularly in the mediastinum)
- whether there is contiguous extranodal involvement (E sites) or disseminated extranodal disease
- whether typical systemic symptoms (B symptoms) are present.

In defining the disease stage, it is important to note how the information was obtained, since this fact reflects on remaining uncertainties in the evaluation for extent of disease. Clinical staging refers to information that has been obtained by initial biopsy, history, physical examination, and laboratory and radiographic studies only. A pathologic stage is determined by more extensive surgical assessment of potentially involved sites, eg, by surgical staging laparotomy and splenectomy.

TABLE 1: The Cotswald's staging classification for Hodgkin's lymphoma

Stage	Description
I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (ie, the mediastinum is a single site, hilar lymph nodes are lateralized). The number of anatomic sites should be indicated by a subscript (eg, II_2).
III	Involvement of lymph node regions or structures on both sides of the diaphragm:
	III_1: With or without involvement of splenic, hilar, celiac, or portal nodes
	III_2: With involvement of para-aortic, iliac, or mesenteric nodes
IV	Involvement of extranodal site(s) beyond that designated E
Designations applicable to any disease stage[a]	
A	No symptoms
B	Fever, drenching sweats, weight loss
X	Bulky disease: > 1/3 the width of the mediastinum > 10 cm maximal dimension of nodal mass
E	Involvement of a single extranodal site, contiguous or proximal to a known nodal site
CS	Clinical stage
PS	Pathologic stage

[a] For examples of how these designations are applied to disease stage, see text discussion.

Also, various designations relating to the presence or absence of B symptoms or bulky disease (see Table 1) can be applied to any disease stage. For example, a patient with no B symptoms but with a bulky mediastinal mass and involvement of the cervical lymph nodes would be defined as having CS IIAX disease. A patient with axillary disease and fever who underwent a staging laparotomy that revealed involvement of the para-aortic lymph nodes and spleen would be staged as PS III_2B.

Most recent studies in stage I/II distinguish between favorable and unfavorable early-stage disease, according to the European Organization for Research and Treatment of Cancer (EORTC) definitions outlined in Table 2.

Clinical staging evaluation

Disease-associated symptoms As mentioned previously, disease-associated symptoms may occur in up to one-third of patients. They may include B symptoms, pruritus, and, less commonly, pain in involved regions after ingestion of alcohol. In each anatomic stage, the presence of B symptoms is an adverse prognostic indicator and may strongly affect treatment choices. B symp-

TABLE 2: EORTC prognostic definition of early-stage disease

Favorable	CS I and II (maximum 3 involved areas) and < 50 years *and* ESR < 50 mm/h (no B symptoms) *or* ESR < 30 mm/h (B symptoms present) *and* MT ratio < 0.33
Unfavorable	CS II ≥ 4 nodal areas involved *or* age ≥ 50 years *or* ESR ≥ 50 mm/h (no B symptoms) *or* ESR ≥ 30 mm/h (B symptoms present) *or* MT ratio ≥ 0.33

CS = Cotswald's staging; EORTC = European Organization for Research and Treatment of Cancer; ESR = erythrocyte sedimentation rate; MT = mediastinal/thoracic.

toms are carefully defined in the staging system. Unexplained fever should be > 38°C and recurrent during the previous month, night sweats should be drenching and recurrent, and unexplained weight loss is significant only if > 10% of body weight has been lost within the preceding 6 months. Although pruritus is no longer considered to be a B symptom, the presence of generalized itching may be considered to be an adverse prognostic symptom.

Certain combinations of B symptoms are more prognostically significant than others. For example, the combination of fever and weight loss has a worse prognosis than do night sweats alone.

Physical examination should carefully determine the location and size of all palpable lymph nodes. Inspection of Waldeyer's ring, detection of splenomegaly or hepatomegaly, and evaluation of cardiac and respiratory status are important.

Laboratory studies should include a CBC with WBC differential and platelet count, the erythrocyte sedimentation rate (ESR), tests for liver and renal function, and assays for serum alkaline phosphatase and lactate dehydrogenase (LDH). A moderate to marked leukemoid reaction and thrombocytosis are common, particularly in symptomatic patients, and usually disappear with treatment.

ESR The ESR may provide helpful prognostic information. At some centers, treatment programs for patients with early-stage disease are influenced by the degree of ESR elevation. In addition, changes in the ESR following therapy may correlate with response and relapse.

Abnormalities of liver function studies should prompt further evaluation of that organ, with imaging and possible biopsy.

Alkaline phosphatase An elevated alkaline phosphatase level may be a nonspecific marker, but it may also indicate bone involvement that should be appropriately evaluated by a radionuclide bone scan and directed skeletal radiographs.

Imaging studies Radiologic studies should include a chest x-ray and CT scan of the chest, abdomen, and pelvis with IV contrast. In most patients, PET scan will provide important information on the extent of disease, and a baseline for evaluation of response to treatment is highly recommended. Radionuclide

TABLE 3: Results of prospective randomized studies with short chemotherapy followed by IFRT for early-stage HL

Study (# of patients)	Prognostic group	Treatment	RFS or FFTF	OS (median follow-up)
Milan (133)	Favorable and unfavorable	ABVD (4) + IFRT (36 Gy)	94%	94% (12 years)
GHSG HD8 (1,064)	Unfavorable	COPP/ABVD (4) + IFRT (30 Gy + 10 Gy to bulk)	84%	92% (5 years)
EORTC H8U (995)	Unfavorable	MOPP/ABV (4) + IFRT (36 Gy)	96%	93% (4 years)
GHSG HD10 (1,131)	Favorable	ABVD (2 or 4) + IFRT (20 or 30 Gy)	97%	99% (2 years)
GHSG HD11 (1,363)	Unfavorable	ABVD (4) or BEACOPP (4) + IFRT (20 or 30 Gy)	90%	97% (2 years)

Abbreviations: For chemotherapy, see Table 4

EORTC = European Organization for Research and Treatment of Cancer; FFTF = freedom from treatment failure; GHSG = German Hodgkin's Study Group; HL = Hodgkin's lymphoma; IFRT = involved-field radiation therapy; OS = overall survival; RFS = relapse-free survival.

bone scan, MRI of the chest or abdomen, and CT scan of the neck are contributory only under special circumstances.

Evaluation for supradiaphragmatic disease The thoracic CT scan details the status of intrathoracic lymph node groups, the lung parenchyma, pericardium, pleura, and chest wall. Since the chest CT scan may remain abnormal for a long time after the completion of therapy, the evaluation of pretreatment involvement and response to therapy is assisted by the use of a PET or gallium scan. ^{18}F-fluorodeoxyglucose (FDG)-PET scanning provides more information and better resolution than does a gallium scan.

Evaluation of the abdomen and pelvis A CT scan and PET are the basic imaging studies for evaluation of the abdomen and pelvis.

Bone marrow biopsy Bone marrow involvement is relatively uncommon, but because of the impact of a positive biopsy on further staging and treatment, unilateral bone marrow biopsy should be part of the staging process of patients with stage IIB disease or higher.

Lymphangiography and staging laparotomy

These two old methods of staging have been replaced by modern imaging techniques using high-resolution CT scanning and FDG-PET.

Treatment

HL is sensitive to radiation and many chemotherapeutic drugs, and, in most stages, there is more than one effective treatment option. Disease stage is the most important determinant of treatment options and outcome. All patients, regardless of stage, can and should be treated with curative intent.

TREATMENT OF STAGE I/II DISEASE

The treatment of choice for favorable and unfavorable early-stage classic HL is brief chemotherapy followed by involved-field radiotherapy (IFRT). Most of the experience that yielded excellent treatment results with low toxicity was with ABVD (Adriamycin [doxorubicin], bleomycin, vinblastine, and dacarbazine [DTIC-Dome]) × 4 and IFRT of 30 to 36 Gy. Table 3 summarizes data from randomized studies that reported on the combination of short chemotherapy (four or even only two cycles) followed by IFRT. The three top randomized studies have also indicated that adding extended-field radiotherapy to chemotherapy is not necessary and the small involved field is adequate.

The most recent (and as yet fully mature) excellent results are with shortening the duration of chemotherapy to only two cycles of ABVD in favorable patients and reducing the IFRT dose to 20 Gy (Table 3). If the excellent results obtained by the German Hodgkin's Study Group prevail with additional follow-up, brief ABVD and low-dose IFRT will become the standard of care for favorable early-stage HL.

Subtotal lymphoid irradiation (ie, treatment of the mantle and para-aortic fields only) remains an adequate alternative treatment of clinically or pathologically staged favorable (nonbulky and without B symptoms) early-stage HL (stage I/II). Yet this option is no longer the treatment of choice due to the risk of second tumors and (to a lesser degree) coronary artery disease in long-term survivors of extensive radiotherapy alone as practiced in the past. In classic (non–lymphocyte predominant) HL, subtotal lymphoid irradiation is adequate for patients who are not candidates for a chemotherapy-containing strategy.

In patients who underwent pathologic staging (laparotomy) and were treated with primary irradiation alone, several large series reported a 15- to 20-year survival rate of nearly 90% and a relapse-free survival rate of 75%-80%. Most relapses (75%) occurred within 3 years after the completion of therapy; late relapses were uncommon. More than half of the patients who relapsed after radiotherapy alone were still curable with standard chemotherapy.

Canadian and European studies have reported excellent overall survival results in patients selected for radiotherapy on the basis of clinical prognostic factors alone. Thus, irradiation alone can be safely offered to clinically staged patients with favorable prognostic factors who are not candidates for combined-modality treatment.

Chemotherapy alone In two prospective, randomized studies, radiotherapy alone was as effective as or superior to MOPP (mechlorethamine [Mustargen], Oncovin [vincristine], procarbazine [Matulane], and prednisone) chemotherapy in improving the survival of patients with early-stage disease. Although the relapse rate after chemotherapy is similar to that after radiotherapy, conventional-dose salvage chemotherapy used after failure of chemotherapy has poor results, which translates into an inferior overall survival.

More recently, five prospective randomized studies compared chemotherapy alone with chemotherapy followed by IFRT or regional radiotherapy in patients with early-stage HL. The Children's Cancer Group (CCG) tested the role of radiation therapy in young patients (< 21 years old) who attained a complete response with risk-adapted chemotherapy (mostly COPP [cyclophosphamide (Cytoxan, Neosar), Oncovin (vincristine), procarbazine, and prednisone)/ABV [Adriamycin (doxorubicin), bleomycin, and vinblastine], four to six cycles). They enrolled 829 patients into the study (68% had early-stage disease); 501 patients who achieved a complete response were then randomized to receive either low-dose (21 Gy) IFRT or no further treatment. The accrual was stopped earlier than planned because of a significantly higher number of relapses on the no-radiotherapy arm. The 3-year event-free survival with an intent-to-treat analysis was 92% for patients randomized to receive radiotherapy and 87% for those randomized to receive no further treatment ($P = .057$).

The EORTC/Groupe d'Etude des lymphomes de l'adulte (GELA) conducted a large randomized trial in patients with favorable early-stage classic HL. All patients received six cycles of EBVP (epirubicin [Ellence], bleomycin, vinblastine, and prednisone). Only patients who achieved a complete response are randomized to receive either IFRT of 36 Gy, IFRT of 20 Gy, or no irradiation. After an interim analysis, the EORTC/GELA groups closed the entry to the no-radiotherapy arm because of the excessive number of relapses.

The National Cancer Institute of Canada and the Eastern Cooperative Oncology Group (ECOG) included 405 patients with nonbulky stage I/II disease. They were randomized to receive either "standard therapy," namely, subtotal nodal irradiation (STNI) for favorable patients, and ABVD (two cycles) followed by STNI for unfavorable (B, elevated ESR, ≥ 3 sites, age ≥ 40, mixed cellularity histology) patients or experimental therapy consisting of six cycles or four cycles (if complete response was attained after two cycles) of ABVD and no radiotherapy. At a median follow-up of 4.2 years, progression-free survival with ABVD alone was significantly inferior ($P = .006$; hazard ratio = 2.6; 5-year estimates of disease progression-free survival, 87% vs 93%). At this early point, no survival difference has been detected.

The Memorial Sloan-Kettering Cancer Center trial included 152 patients with nonbulky early-stage HL. Patients were randomized up front to receive either ABVD × 6 alone or ABVD × 6 followed by radiotherapy. At 60 months, the duration of complete response and freedom from disease progression for ABVD and radiotherapy vs ABVD alone are 91% vs 87% ($P = .61$) and 86% vs 81% ($P = .61$), respectively. Overall survival was 97% with ABVD and radiotherapy vs 90% with ABVD alone ($P = .08$). Although the differences between the out-

come of the two treatment groups were not statistically significant, the study was not powered to detect differences between the treatment strategies that were smaller than 20%, due to the small number of patients and events.

In a prospectively randomized study reported from India, patients with HL who achieved a complete response after ABVD were randomized to receive either IFRT or no further therapy. The 8-year event-free survival and overall survival were significantly better for the patients who received consolidation with IFRT than for those who received ABVD alone. Subset analysis indicated that the benefit from added IFRT was more prominent in advanced stage than in early stage.

The National Comprehensive Cancer Network (NCCN) guidelines recommend combined-modality therapy as the treatment of choice for favorable or unfavorable classic HL. Opinions differ as to the use of chemotherapy alone and it remains highly controversial.

TECHNICAL ASPECTS OF RADIATION THERAPY

Involved-field radiotherapy

In a combined-modality setting, irradiation of the involved lymph node chain, with or without adjacent sites, and tailoring of the field borders to the postchemotherapy tumor volume (in critical areas such as the mediastinum) are recommended. IFRT is the most appropriate irradiation approach after chemotherapy. IFRT or regional radiotherapy alone is used for lymphocyte-predominant HL. Recommendations for IFRT for HL are detailed in an article by Yahalom and Mauch.

Extended radiation fields

Successful therapy with irradiation alone in classic HL requires treatment of all clinically involved lymph nodes and all nodal and extranodal regions at risk for subclinical involvement (Figure 2). The HL radiation fields were designed to conform to the philosophy of treating regions beyond the immediately involved area while accounting for normal tissue tolerance and the technical constraints of field size. The extended radiation fields are inappropriate when radiation is administered as consolidation following chemotherapy and thus are rarely used today.

Dose considerations

When irradiation alone is used to treat HL, the standard total dose to each field is 3,600 cGy, delivered in daily fractions of 180 cGy over 4 weeks. In addition, clinically involved areas are given a boost of 360-540 cGy in 2-3 fractions to bring the total dose to these areas up to 3,960-4,140 cGy. Patients who receive irradiation as consolidation after chemotherapy receive a total dose of 2,000-3,600 cGy in 150-180-cGy fractions. We normally use opposed anterior and posterior fields that are evenly weighted and treat both fields daily. Three-dimensional conformal radiotherapy and intensity-modulated radiation therapy (IMRT) are employed for selected cases.

SIDE EFFECTS AND COMPLICATIONS OF RADIOTHERAPY

Side effects of radiotherapy depend on the irradiated volume, dose administered, and technique employed. They are also influenced by the extent and type of prior chemotherapy, if any, and by the patient's age.

Acute effects The potential acute side effects of involved fields in the upper body include mouth dryness, change in taste, pharyngitis, nausea, dry cough, dermatitis, and fatigue. These side effects are usually mild and transient.

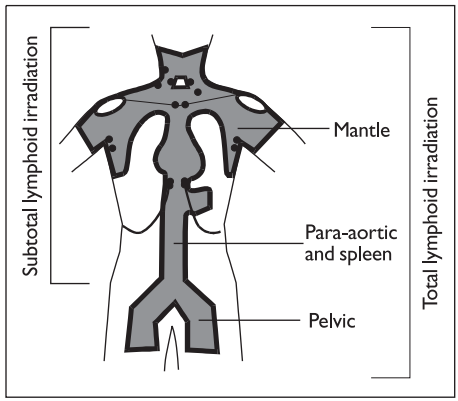

FIGURE 2: Extended radiation fields used for treatment of classic Hodgkin's lymphoma with irradiation alone

The main potential side effects of subdiaphragmatic irradiation are loss of appetite, nausea, and increased bowel movements. These reactions are usually mild and can be minimized with standard antiemetic medications.

Irradiation of more than one field, particularly after chemotherapy, can cause myelosuppression, which may necessitate treatment delays.

The German Hodgkin's Lymphoma Study Group published the final analysis of its randomized trial of COPP/ABVD vs standard BEACOPP vs increased-dose BEACOPP for advanced-stage HL. The CR percentages were 85%, 88%, and 96% for COPP/ABVD, standard BEACOPP, and increased-dose BEACOPP, respectively. The 5-year freedom from treatment failure (69% COPP/ABVD, 76% standard BEACOPP, 87% increased-dose BEACOPP) and overall survival (83% COPP/ABVD, 88% standard BEACOPP, 91% increased-dose BEACOPP) were significantly superior statistically for increased-dose BEACOPP, although more acute myelosuppression was seen with this regimen. Also of some concern, the 5-year actuarial risk of secondary acute leukemia was 0.4% for COPP/ABVD, 0.6% for standard BEACOPP, and 2.5% for increased-dose BEACOPP (P=.03) (*Diehl V, Franklin J, Pfreundschuh M, et al: N Engl J Med 348:2386-2395, 2003*).

Delayed effects Delayed side effects may develop anywhere from several weeks to several years after the completion of radiotherapy.

Lhermitte's sign Approximately 15% of patients who receive the full dose of radiation to the neck may note an electric shock sensation radiating down the backs of both legs when the head is flexed (Lhermitte's sign) 6 weeks to 3 months after mantle-field radiotherapy. Possibly secondary to transient demyelinization of the spinal cord, Lhermitte's sign resolves spontaneously after a few months and is not associated with late or permanent spinal cord damage.

Pneumonitis and pericarditis During the same period, radiation pneumonitis and/or acute pericarditis may occur in < 5% of patients who receive large fields of radiation to the medi-

astinum; these side effects occur more often in those who have extensive mediastinal disease. Both inflammatory processes have become rare with modern radiation techniques.

Herpes zoster infection Patients with HL, regardless of treatment type, have a propensity to develop herpes zoster infection within 2 years after therapy. Usually, the infection is confined to a single dermatome and is self-limited. If the cutaneous eruption is identified promptly, treatment with systemic acyclovir will limit its duration and intensity.

Subclinical hypothyroidism Radiotherapy of the neck can induce subclinical hypothyroidism in about one-third of patients. This condition is detected by elevation of thyroid-stimulating hormone (TSH). Thyroid replacement with levothyroxine (T_4) is recommended, even in asymptomatic patients, to prevent overt hypothyroidism and decrease the risk of benign thyroid nodules.

Infertility Irradiation of the pelvis may have deleterious effects on fertility. In most patients, this problem can be avoided by appropriate gonadal shielding. In females, the ovaries can be moved into a shielded area laterally or inferomedially near the uterine cervix. Irradiation fields that spare the pelvis do not increase the risk of sterility.

Secondary malignancies Patients with HL who were cured with radiotherapy and/or chemotherapy have an increased risk of secondary solid tumors (most commonly, lung, breast, and stomach cancers, as well as melanoma) and NHL 10 or more years after treatment. Chemotherapy combinations that do not include alkylating agents or a new brief program (such as Stanford V) as well as the smaller involved fields and lower doses are less likely to have the increased risk observed with extended fields and/or MOPP or MOPP-like chemotherapy.

Lung cancer Patients who are smokers should be strongly encouraged to quit the habit because the increase in lung cancer that occurs after irradiation or chemotherapy with alkylating agents has been detected mostly in smokers. Alkylating agents (such as in the MOPP regimen) and radiation therapy were associated with an increased risk of lung cancer in an additive and dose-dependent fashion. These effects were multiplied by tobacco use (see Suggested Reading).

Breast cancer The increase in breast cancer risk is inversely related to the patient's age at HL treatment; no increased risk has been found in women irradiated after 30 years of age. The risk of breast cancer is increased with higher radiation breast dose and is reduced in patients who received chemotherapy or ovarian irradiation that induced early menopause. In a case-controlled study performed at The Netherlands Cancer Institute, 48 women with breast cancer after HL were matched with 175 women with HL and no breast cancer. The study demonstrated that women who received chemotherapy followed by radiation therapy had a significantly decreased relative risk (RR) of developing breast cancer as compared with patients treated with irradiation alone (RR = 0.45; $P = .005$). For patients treated with irradiation alone, the risk of breast cancer increased significantly with increasing radiation dose to the breast (P trend = .01). Reaching menopause before the age of 35 years after treatment

TABLE 4: Chemotherapeutic regimens used for the treatment of Hodgkin's lymphoma

Regimen	Dosage and schedule	Frequency
MOPP		
Mechlorethamine	6 mg/m^2 IV on day 1	
Oncovin	1.4 mg/m^2 IV on day 1 (maximum dose, 2.0 mg)	
Procarbazine	100 mg/m^2 PO on days 1-7	*Repeat cycle*
Prednisone[a]	40 mg/m^2 PO on days 1-14	*every 28 days.*
ABVD		
Adriamycin	25 mg/m^2 IV on days 1 and 15	
Bleomycin	10 mg/m^2 IV on days 1 and 15	
Vinblastine	6 mg/m^2 IV on days 1 and 15	*Repeat cycle*
Dacarbazine	375 mg/m^2 IV on days 1 and 15	*every 28 days.*
BEACOPP		
Bleomycin	10 mg/m^2 IV on day 8	
Etoposide	100 mg/m^2 (200 mg/m^2)[d] IV on days 1-3	
Adriamycin	25 mg/m^2 (35 mg/m^2)[d] IV on day 1	
Cyclophosphamide	650 mg/m^2 (1,200 mg/m^2)[d] IV on day 1	
Oncovin	1.4 mg/m^2[e] IV on day 8	
Procarbazine	100 mg/m^2 PO on days 1-7	
Prednisone	40 mg/m^2 PO on days 1-14	*Repeat cycle*
G-CSF from day 8		*every 21 days*
Stanford V		
Doxorubicin	25 mg/m^2 IV on days 1 and 15	*Repeat cycle*
Vinblastine[b]	6 mg/m^2 IV on days 1 and 15	*every 28 days for*
Mechlorethamine	6 mg/m^2 IV on day 1	*a total of 3 cycles.*
Vincristine[b]	1.4 mg/m^2 IV[c] on days 8 and 22	*Radiotherapy to*
Bleomycin	5 U/m^2 IV on days 8 and 22	*initial sites ≥ 5 cm*
Etoposide	60 mg/m^2 IV on days 15 and 16	*(dose: 36 cGy).*
Prednisone	40 mg/m^2 PO every other day (maximum dose, 2.0 mg)	

[a] In the original report, prednisone was given only in cycles 1 and 4.

[b] Vinblastine dose decreased to 4 mg/m^2 and vincristine dose to 1 mg/m^2 during cycle 3 for patients ≥ 50 years of age.

[c] Tapered by 10 mg every other day starting at week 10.

[d] Increased dose for BEACOPP.

[e] Maximal dose of 2 mg.

G-CSF = granulocyte colony-stimulating factor.

with chemotherapy and irradiation was associated with a markedly reduced risk of breast cancer (RR = 0.06; P = .001). The risk reduction with combined-modality treatment indicates the importance of ovarian function in the tumorigenesis process of radiation-induced breast cancer. A larger international case-controlled study of 105 breast cancer patients and 266 controls had similar findings.

In most situations, modern involved-field radiotherapy should spare the breast. Breast cancer is curable in its early stages, and early detection has a significant impact on survival. Breast examination should be part of the routine follow-up for women cured of HL, and routine mammography should begin about 8 years after treatment.

In a recent study, detailed cardiovascular testing and quality-of-life evaluation were performed on 48 patients treated for HL during childhood or adolescence, with a median follow-up of 14 years. Although no patient had symptomatic heart disease at screening, all but one had cardiac abnormalities on screening. Restrictive cardiomyopathy was suggested, and significant valvular defects were present in 42%; 75% of patients had conduction defects. The authors concluded that a variety of unsuspected, clinically significant cardiovascular abnormalities are common in long-term survivors of HD who are treated at a young age with mediastinal irradiation (*Adams MJ, Lipsitz SR, Colan SD, et al: J Clin Oncol 22:3139-3148, 2004*).

Cardiovascular disease An increased risk of cardiovascular morbidity has been reported among patients who have received mediastinal irradiation. In a retrospective study evaluating the cardiac risks of 450 patients cured of HL with radiotherapy alone or in combination, 42 patients (10%) developed coronary artery disease (CAD) at a median of 9 years after treatment, 30 patients (7%) developed carotid and/or subclavian artery disease at a median of 17 years after treatment, and 25 patients (6%) developed clinically significant valvular dysfunction at a median of 22 years. The most common valve lesion was aortic stenosis, which occurred in 14 valves. The only treatment-related factor associated with the development of CAD was use of a radiation technique that resulted in a higher total dose to a portion of the heart (RR = 7.8; 95% CI = 1.1-53.2; P=.04). No specific treatment-related factor was associated with carotid or subclavian artery disease or valvular dysfunction. Freedom from any cardiovascular morbidity was 88% at 15 years and 84% at 20 years.

The Late Effects Study Group reported that in children treated at an age younger than 16 years and followed for a median of 17 years from treatment of HL, the risk of second neoplasms was increased 18.5-fold compared with the general population, and the cumulative risk of solid malignancies at 20 years was 7% and of all second malignancies (including leukemia), 10%. Breast cancer was the most common solid tumor, and thyroid cancer, bone malignancies, colorectal cancer, lung cancer, and gastric cancer were also common. Risk factors for second solid tumors included a young age at diagnosis of HL and treatment including radiation therapy. The incidence of third malignancies approached 21% at 10 years from the diagnosis of the second malignancy. Surveillance of the population at high risk is encouraged (*Bhatia S, Yasui Y, Robison LL, et al: J Clin Oncol 21:4386-4394, 2003*).

To reduce this hazard, radiation fields should conform to the involved postchemotherapy volume, and the dose should be reduced to 20-30 Gy if possible. Patients who have received radiation to the mediastinum should be moni-

TABLE 5: Toxicities associated with combination chemotherapy and radiation therapy

Acute toxicities

- Alopecia
- Nausea and vomiting
- Diarrhea
- Mucositis
- Paresthesias and neuropathies
- CNS confusion
- Anemia, leukopenia, and thrombocytopenia
- Disulfiram-like reaction following alcohol while taking procarbazine

Delayed toxicities

- Secondary malignancies
  - Acute myelogenous leukemia
  - Acute lymphocytic leukemia
  - Non-Hodgkin's lymphoma
  - Melanoma
  - Sarcoma
  - Breast, gastric, lung, and thyroid cancers
- Endocrine complications
  - Infertility
  - Hypothyroidism
- Pulmonary complications
  - Bleomycin-related lung toxicity
  - Pulmonary fibrosis
- Cardiac complications
  - Cardiomyopathy
    - Accelerated atherosclerotic heart disease
    - Pericardial fibrosis

tored and advised about other established coronary disease risk factors, such as smoking, hyperlipidemia, hypertension, and poor dietary and exercise habits. Cholesterol levels should be monitored and treated if elevated.

Effects on bone and muscle growth In children, high-dose irradiation will affect bone and muscle growth and may result in deformities. Current treatment programs for pediatric HL are chemotherapy-based; radiotherapy is limited to low doses.

TREATMENT OF STAGE III/IV DISEASE

Chemotherapy has become curative for many patients with advanced stages of HL. MOPP has been the primary effective combination chemotherapy regimen for advanced-stage disease since the 1960s. Over the past several years, ABVD has been shown to be more effective and less toxic than MOPP, particularly with respect to sterility and secondary leukemia.

Combination chemotherapy regimens

Doxorubicin-containing regimens A doxorubicin-containing regimen, such as ABVD (Table 4), is the treatment of choice for patients presenting with stage III or IV disease, as demonstrated by a randomized phase III trial undertaken by the Cancer and Leukemia Group B (CALGB). This trial showed higher complete response rates with ABVD and ABVD/MOPP (82% and 83%, respectively) than with MOPP alone (65%).

One reason for the improved response rate in the groups treated with doxorubicin-containing regimens was the higher percentage of patients who were able to receive ≥ 85% of the expected chemotherapy dose, particularly in the ABVD group. In addition, rates of significant and life-threatening neutropenia were higher in patients treated with the MOPP-containing regimens than in those treated with other regimens.

Subsequent trials compared ABVD, alternating MOPP/ABVD, and a MOPP/ABV hybrid. Alternating MOPP/ABVD and the MOPP/ABV hybrid were found to be equally effective in treating advanced-stage HL. However, a recent intergroup study that compared ABVD with MOPP/ABV hybrid (without irradiation) was closed early because of concerns of excess treatment-related deaths and second malignancies (mostly acute myelogenous leukemia and lung cancer) in the MOPP/ABV hybrid arm.

In a recent update of the Stanford V chemoradiotherapy program, 256 patients with classic HL were treated on prospective trials with the weekly Stanford V (see Table 4) regimen ± radiotherapy (RT). In all patients, freedom from disease progression was 91% at 8 years and 89% at 12 years, and overall survival rates were 95% at 8 and 12 years. Among 24 patients with disease progression, 16 (67%) were successfully treated with second-line therapy. No cases of secondary myelodysplasia/leukemia or non-HL have occurred. To date, 72 post-treatment conceptions (excluding pretreatment semen or embryo cryopreservation) were recorded, with 65 live births (plus 4 current pregnancies) among 34 men and 30 women. In our hands, the Stanford V and RT regimen was effective with modest toxicity, and 25% of patients conceived post-treatment *(Horning SJ, Hoppe RT, Advani R, et al: Blood 104:abstract 308, 2004).*

Shortened dose-intense regimens Recently, shortened dose-intense regimens have shown promise. For example, the 12-week Stanford V regimen (see Table 4) combined with IFRT produced a 5-year overall survival rate of 96% and a freedom-from-disease-progression rate of 89%. The freedom-from-disease-progression rate was significantly superior among patients with a prognostic score of 0-2, compared with those with a score of 3 and higher (94% vs 75%; $P = .0001$). Of interest, in 142 patients from Stanford, no secondary leukemia was observed, and 42 pregnancies were reported.

In the intergroup trial, 856 patients with advanced-stage HL were randomized to undergo treatment with ABVD or MOPP/ABV hybrid chemotherapy. There were no significant differences in the rates of CR (76% vs 80%, $P = .16$) or 5-year failure-free (63% vs 66%, $P = .42$) or overall (82% vs 81%, $P = .82$) survival. However, MOPP/ABV hybrid chemotherapy was associated with significantly greater incidences of acute pulmonary and hematologic toxicity, myelodysplastic syndromes, and leukemias than ABVD *(Duggan DB, Petroni GR, Johnson JL, et al: J Clin Oncol 21:607-614, 2003).*

Another new regimen called BEACOPP (bleomycin, etoposide, Adriamycin [doxorubicin], cyclophosphamide, Oncovin [vincristine], procarbazine, and prednisone) combined with IFRT (in most patients) showed better results than did COPP/ABVD in studies by the German Hodgkin's Lymphoma Study Group.

Combined-modality therapy

Although the role of consolidation radiotherapy after induction chemotherapy remains controversial, irradiation is routinely added in patients with advanced-stage disease who present with bulky disease or who remain in uncertain complete remission after chemotherapy. Retrospective studies have demonstrated that adding low-dose radiotherapy to all initial disease sites after chemotherapy-induced complete response decreases the relapse rate by ~25% and significantly improves overall survival.

Interpretation of the impact of irradiation in prospective studies has been controversial. However, a Southwest Oncology Group (SWOG) randomized study of 278 patients with stage III or IV HL suggested that the addition of low-dose irradiation to all sites of initial disease after a complete response to MOP-BAP (mechlorethamine, Oncovin [vincristine], prednisone, bleomycin, Adriamycin [doxorubicin], and procarbazine) chemotherapy improves remission duration in patients with advanced-stage disease. An intention-to-treat analysis showed that the advantage of combined-modality therapy was limited to patients with nodular sclerosis. No survival differences were observed.

A recent meta-analysis demonstrated that the addition of radiotherapy to chemotherapy reduces the rate of relapse but did not show a survival benefit for the combined-modality approach.

LONG-TERM TOXICITIES OF COMBINATION CHEMOTHERAPY

The CALGB trial and the intergroup trials mentioned previously (see section on "Combination chemotherapy regimens") noted differences in the long-term toxicities of various combination chemotherapeutic regimens (Table 5).

Myelodysplasia and acute leukemia MOPP therapy is known to be related to the development of myelodysplastic syndromes (MDS) and acute leukemia. These secondary hematologic malignancies begin 2 years following therapy and decline by 10 years, with the maximum risk between 5 and 9 years. Patients with these malignancies have a poor prognosis.

The incidence of secondary leukemia appears to increase with cumulative doses of chemotherapy, age > 40 years when receiving chemotherapy for HL, and splenectomy. It is controversial whether combined-modality therapy increases the risk of leukemia compared with chemotherapy alone.

Cytogenetic studies of secondary leukemias reveal a loss of the long arm of chromosome 5 and/or 7. Less frequently, there is a loss of chromosome 18 or rearrangement of the short arm of chromosome 17. A balanced rearrangement of 11q23 and 2lq22 also has been described with etoposide therapy.

Other malignancies also are being observed with increasing frequency after chemotherapy (most regimens included alkylating agents), particularly lung cancer and NHL. These malignancies have a longer latency period and usually are not observed until 15 years after therapy.

Infertility is another long-term complication seen with combination chemotherapy. At least 80% of males are found to have permanent azoospermia or oligospermia following more than three cycles of MOPP chemotherapy; < 10% of men will have recovery of spermatogenesis within 1-7 years following the end of chemotherapy. The risk of infertility with ABVD chemotherapy is significantly lower than that with MOPP chemotherapy, approximately 15%-25%. All men who desire childbearing potential following therapy should be counseled regarding sperm banking.

In females, there is a 50% rate of primary ovarian failure overall. The risk is 25%-30% in patients treated at age 25 or younger but increases to 80%-100% in women older than age 25. Many women who do maintain ovarian function during chemotherapy will have premature menopause following therapy.

Pulmonary complications have been reported with ABVD chemotherapy and are related to bleomycin-induced lung toxicity. In a Memorial Sloan-Kettering Cancer Center study of 60 patients with early-stage HL receiving ABVD chemotherapy with or without mediastinal irradiation, 53% reported dyspnea on exertion or cough during ABVD chemotherapy and 37% had a significant decline in pulmonary function. Bleomycin was discontinued in 23% of patients. Following ABVD therapy, there was a significant decline in median forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). Radiotherapy following ABVD chemotherapy resulted in a further decrease in FVC but did not significantly affect functional status. At longer follow-up, only 1 of 60 patients reported persistent dyspnea on minimal exertion.

In the CALGB trial, there were 3 fatal pulmonary complications in 238 patients; all 3 patients were older than age 40.

Pulmonary fibrosis has also been described after combined-modality therapy. Pulmonary function testing usually reveals a decreased diffusion capacity and restrictive changes prior to the onset of symptoms.

Cardiomyopathy is a recognized complication of doxorubicin therapy but is not commonly seen in patients receiving ABVD chemotherapy. Patients who are treated with six cycles of ABVD chemotherapy receive a total doxorubicin dose of 300 mg/m^2; cardiac toxicity is rarely seen in patients who receive a total dose ≤ 400 mg/m^2.

The final results of the EORTC trial that evaluated the role of low-dose IFRT (up to 24 Gy) in patients with stage III/IV HL who achieved a CR after 6-8 cycles of MOPP/ABV hybrid chemotherapy have been reported. Most patients who achieved a PR received IFRT up to 30 Gy. Of 739 patients, 421 had a CR and 333 of them were randomized to receive either IFRT (161 patients) or no further treatment (172 patients). The median follow-up was 79 months. The 5-year event-free survival rate was 84% for the group receiving no further treatment and 79% for the group receiving IFRT (*P*=.35), and the 5-year overall survival rates were 91% and 85%, respectively (*P*=.07). The 5-year event-free survival rate was 79% and the 5-year overall survival rate was 87% for patients achieving a PR after chemotherapy. IFRT did not improve the outcome for patients who achieved a CR after chemotherapy, but it benefited those who achieved only a PR *(Aleman BM, Raemaekers JM, Tirelli U, et al: N Engl J Med 348:2396-2406, 2003).*

A recent report from Memorial Sloan-Kettering Cancer Center included integrated analysis of 75 consecutive patients with biopsy-confirmed primary refractory HD who were treated with high-dose chemoradiotherapy and ASCT. At a median follow-up of 10 years, the event-free survival (EFS), disease progression-free survival (PFS), and overall survival (OS) rates were 45%, 49%, and 48%, respectively. Only chemosensitivity to standard-dose second-line chemotherapy (SDSC) predicted for a better survival, thus responding patients had an EFS, PFS, and OS of 60%, 62%, and 66%, respectively, vs 19%, 23%, and 17% for patients who had a poor response to SDSC ($P < .001$). Novel approaches are needed to cure patients with HL for whom both front-line and second-line chemotherapy fails *(Moskowitz CM, Kewalramani T, Nimer SD, et al: Br J Haematol 124;645-652, 2004).*

MANAGEMENT OF RELAPSED DISEASE

Relapse after radiation therapy

Patients with early-stage HL who relapse after initial therapy with irradiation alone have excellent complete remission rates and 50%-80% long-term survival rates when treated with MOPP or ABVD. The dose regimens used for salvage therapy are the same as those outlined in Table 4.

Relapse after combination chemotherapy

Among patients with advanced-stage HL, 70%-90% will have complete response to treatment; however, up to one-third of patients with stage III or IV disease will relapse, usually within the first 3 years after therapy.

Various studies have identified the following poor prognostic factors for response to first-line chemotherapy: B symptoms, age > 45 years, bulky mediastinal disease, extranodal involvement, low hematocrit, high ESR, high levels of CD30, and high levels of serum interleukin-10 and soluble IL-2 receptor.

An International Prognostic Index (IPI) has been devised for advanced HL based on a retrospective analysis of 1,618 patients from 25 centers. In the final model, seven factors were used: albumin < 4 g/dL, hemoglobin < 10.5 g/dL, male gender, stage IV disease, age ≥ 45 years, WBC ≥ 15,000/µL, and lymphocytes < 600/µL (or 8% of the WBC count). The worst prognostic group (7%) had a 5-year overall survival rate of 56% and a failure-free survival rate of 42%.

In a comparison of seven well-known prognostic models for HL applied retrospectively to a population of patients with advanced-stage disease, three were found to be the most predictive of outcome. One was the IPI, mentioned previously. The other two were the Memorial Sloan-Kettering Cancer Center model (employing age, LDH, hematocrit, inguinal nodal involvement, and mediastinal mass bulk) and the Database on Hodgkin's Disease model (employing stage, age, B symptoms, albumin, and gender). Integration of the three models in a linear model improved their predictive power.

High-dose therapy with autologous stem-cell transplantation The preferred salvage method for patients who relapsed after combined-modality therapy or chemotherapy alone or remained refractory to those programs is high-dose chemoradiotherapy with autologous stem-cell transplantation (ASCT).

Two randomized studies (from Great Britain and Germany) demonstrated an event-free survival advantage with the high-dose therapy approach. Although a significant survival advantage was not observed due to the crossover design of the studies, most patients with refractory disease or postchemotherapy relapse are currently managed with high-dose chemoradiation therapy and ASCT.

No standard conditioning regimen has been used in this setting, as patients have had prior treatment with a variety of combinations of chemotherapy and radiation therapy. Although most patients who have received bone marrow have been treated with several regimens or have had poorly responsive disease from initial diagnosis, the complete response rate has ranged from 50%-80%, with approximately 40%-80% of responding patients achieving durable remission.

Recent analysis of prognostic factors in patients receiving high-dose salvage therapy indicated that B symptoms at relapse, extranodal disease, and short (< 1 year) remission or no remission are factors associated with a poor outcome.

A recent study from Memorial Sloan-Kettering Cancer Center reported the results of high-dose chemotherapy with ASCT in 65 patients with relapsed or refractory HL. At a median follow-up of 43 months, overall survival was estimated to be 73% and event-free survival was estimated to be 58% by intent-to-treat analysis. In a multivariate logistic regression model, there were three adverse prognostic factors: extranodal sites of relapse or refractory disease, complete remission duration of less than 1 year or refractory disease, and B symptoms. Patients with no or one adverse factor had an overall survival of 90% and an event-free survival of 83%. Patients with two adverse factors had an overall survival of 57% and an event-free survival of 27%; those with three adverse factors had an overall survival of 25% and an event-free survival of 10%. A follow-up study of a risk-adapted approach based on the study previously described suggested that patients with adverse prognostic factors may benefit from further augmentation of high-dose programs, including a "double-transplant" for selected patients.

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